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Cholinesterase inhibitors: new roles and therapeutic alternatives

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Abstract

An important aspect of brain cholinesterase function is related to enzymatic differences. The brain of mammals contains two major forms of cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). The two forms differ genetically, structurally and for their kinetics. Butyrylcholine is not a physiological substrate in mammalian brain which makes the function of BuChE of difficult interpretation. In human brain, BuChE is found in neurons and glial cells as well as in neuritic plaques and tangles in Alzheimer disease (AD) patients. While AChE activity decreases progressively in the brain of AD patients, BuChE activity shows some increase. In order to study the function of BuChE, we perfused intracortically the rat brain with a selective BuChE inhibitor and found that extracellular acetylcholine increased 15 fold from 5 to 75 nM concentrations with little cholinergic side effects in the animal. Based on these data and on clinical data showing a relation between CSF BuChE inhibition and cognitive function in AD patients, we postulated that two pools of cholinesterases may be present in brain, the first mainly neuronal and AChE dependent and the second mainly glial and BuChE dependent. The two pools show different kinetic properties with regard to regulation of ACh concentration in brain and can be separated with selective inhibitors. Within particular conditions, such as in mice nullizygote for AChE or in AD patients at advanced stages of the disease, BuChE may replace AChE in hydrolyzing brain acetylcholine.

Based on the changes of ChE activity in the brain of AD patients, a rational indication of selective BuChEI (or of mixed double function inhibitors) is the treatment of advanced cases. A second novel aspect of ChEI therapy is the emerging of new indications which include various forms of dementia such as dementia with Lewy Bodies, Down Syndrome, vascular dementia and Parkinson Dementia. Clinical results demonstrate examples of versatility of cholinergic enhancement.

Keywords: Alzheimer disease; Butyrylcholinesterase; Cholinesterase inhibitors; Down Syndrome; Dementia with Lewy bodies; Parkinson dementia; Vascular dementia; Delirium; Traumatic brain injury

1. Introduction

The most significant therapeutic effect of cholinesterase inhibitors (ChE) in Alzheimer disease (AD) treatment is to stabilize cognitive function at a steady level during at least 1-year period in approximately 50% patients. Most clinical studies show that in a certain percentage of AD patients (approximately 20%) cognitive function can be stabilized for a period of up to 24 months. In addition, the AD patients who do not respond to therapy with one ChEI can be switched to a second one with a 50% rate of success. New findings show that both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are involved in the breakdown of acetylcholine in the brain and dual inhibition of these enzymes may increase the efficacy of treatment and broaden the indications.

This review will consider two new aspects of ChEI treatment. The first is related to the presence of the enzyme BuChE in brain, its possible function and its significance in the therapeutic approach to AD. The second aspect is related to new indications of ChEI therapy in a variety of CNS disorders from Down Syndrome (DS) to traumatic brain injury (TBI) or delirium. The effect of ChEI on such a broad spectrum of CNS disorders suggests either a general activation of brain mechanisms during cholinergic enhancement or multiple mechanisms of action.

2. The rediscovery of a brain enzyme

2.1. Role of BuChE in normal brain and in Alzheimer's disease

"Of the many questions about pseudocholinesterases that remain unanswered perhaps the most puzzling is the

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